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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/878,131	HONG ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 18-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 18-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on August 02, 2005 has been entered.

Status of the Application

2. Claims 1-11, 18-35 are pending. Claims 1, 9, 10, 22 and 30 are amended. All amendments and arguments have been thoroughly reviewed and deemed persuasive in part for the reasons that follow. This action is made Final.

3. The following rejections are made inn the previous office action:

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 18-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant independent claims 1-3, 6-11, 20-23, 26-31, 34-35 are drawn to a method for extending an oligonucleotide comprising mixing a template DNA with a primer or primers and a natural or a modified form of a moderately thermostable DNA polymerase from an organism selected from the group consisting of Bacillus stearothermophilus (Bst), Bacillus caldotenax and Bacillus caldolyticus. Further the dependent claims 4, 18-19, 24-25, 32-33 are drawn to the DNA polymerase having at least 95% homology to the amino acid sequence of SEQ ID NO. 3 and 4. The specification has described one species of the organisms, that is, a Bst strain 20 (see instant specification page 11-12) and does not support any other DNA polymerases (other than Bst strain 320) of different species of organisms recited in the instant claims. Further the

specification provides support for a DNA polymerase derived from the Bst strain 320 and does not describe any other DNA polymerases having 95% homology with the full length sequence of the said DNA polymerase. The instant claims include a large number of DNA polymerases and fragments of said large genus. This large genus of fragments is represented in the specification by Bst strain 320 (SEQ ID NO.1 and 2). The specification fails to support any DNA polymerase(s) from organisms Bacillus caldotenax and Bacillus caldolyticus. Thus, applicants have expressed possession of only one species in a genus, which comprises hundreds of different possibilities. The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the structural information (sequences) are disclosed. With regard to the natural or modified form of DNA polymerases, it is insufficient to demonstrate identity of any biological activity, wherein no structural information regarding where in the polynucleotide the activity resides. Further no information is given regarding a methodology to determine such common elements or attributes. Further, there is no description of fragments or variants (derived by substitution, deletion, or insertion) containing the DNA polymerase activity.

With regard to the written description, the instant claims encompass different structural limitations, for which, no support is provided in the specification. It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision

detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In this application at the time of filing, there is no record or description, which would demonstrate conception or written description of any structural information of DNA polymerase from any organism as recited in the instant claims, except for the DNA polymerase from Bst strain 320, with retaining correlative function in the claimed product.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Note: In the following Double Patenting rejections, Claim 1 recites "wherein the DNA polymerase has proofreading activity ..... in a solution containing between about 10% and about 20% (v/v) glycerol or ethylene glycol or a mixture of glycerol and ethylene glycol" which is considered as inherent in the DNA polymerase composition provided in the patented claims, because the "wherein" clause indicates that the DNA polymerase functions in said solution as recited and the property as recited in the instant claims and that of the patented claims is the same, thus the patent inherently teaches said solution, in order to function as disclosed in the patented claims.

A. Claims 1-3, 6-7, and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-23 of U.S. Patent No. 5,834,253 ('253) in view of Iakobashvili et al. (Nucleic Acids Research, Vol. 27, No.6, page 1566-1568, 1999, the reference taken from the IDS submitted on April 4, 2005, by Applicants).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-3, 6-7 are drawn to a method fro extending an oligonucleotide primer or a primer pair using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C, comprising (i) mixing a template DNA with a primer or a pair of primers, and a natural or modified form of a moderately thermostable DNA polymerase selected from the group consisting of Bacillus stearothermophilus, Bacillus caldotenax and Bacillus caldolyticus, wherein the DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminus of the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template, in a solution containing between 10% and about 20% (v/v) glycerol, ethylene glycol, or a mixture of glycerol and ethylene glycol, under conditions that the cycle reaction temperature fluctuates between a melting temperature of about 70^0 C, and an annealing temperature of about 37^0 C, and repeating the cycle primer extension at least two times and until the DNA polymerase repeatedly extends the primer or primer pair of primers to produce a sequence-specific amplification product of a desired length.

Further Claim 20 is drawn to a DNA polymerase having SEQ ID No. 2.

Claims 1-3, 6-7, 20, of the instant invention fall with in the scope of the claims 22-23 of the patent ('253), because the claim 22-23 of the patent disclose said method for extending a primer or primers and replicating a DNA strand using a DNA polymerase having 3'-5' exonuclease activity and said DNA polymerase comprising SEQ ID 2 as recited in the instant application. The patented claims differ from the instant claims in that, the patented claims fail to disclose primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C, under conditions that the cycle reaction temperature fluctuates between a melting temperature of about 70^0 C, and an annealing temperature of about 37^0 C, and repeating the cycle primer extension at least two times and until the DNA polymerase repeatedly extends the primer or primer pair of primers to produce a sequence-specific amplification product of a desired length and use of forward and reverse primers.

Iakobashvili et al. teach a method for extending an oligonucleotide primer or primers using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C (see page 1567, col. 1, Fig. 3, line 1-23 of the legend, indicates melting temperature as 70^0 C and annealing at 37^0 C), comprising the step of mixing a template DNA with primers and a DNA polymerase having proofreading 3'-5' exonuclease activity (which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand) (see page 1567, col. Fig. 3 legend) in a solution containing glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig. 3 legend, which meets the limitations between about 10% and about 20% v/v), under conditions that cycle reaction temperature fluctuates between a melting temperature of about 70^0 C and an annealing temperature about 37^0 C (see page 1567, col. 1, line 21-22 of Fig. 3 legend) and repeating the cycle primer extension reaction

at least two times (repeated 35 cycles) and until the DNA polymerase repeatedly extends the primers to produce a sequence-specific amplification product of a desired length (see page 1567, col. 1, line 21-23 of Fig. 3 legend and also see the Fig .3 for the desired length of sequence-specific product). Iakobashvili et al. teach that the method comprises about 15 % glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig.3, legend, which meets the limitation of about 15%); With regard to claim 6-7, Iakobashvili et al teach use of a forward and a reverse primer to amplify a selected segment of the template by repeated heating and cooling cycles (see page 1567, col. 1, Fig. 3, line 1-9 of the legend); that primers may be of varying length (see page 1566, col. 1, paragraph 3, col. 2, line 1- 14, page 1567, Fig. 4 legend).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for extending an oligonucleotide primer as disclosed by Hong et al. with the temperature conditions ranging between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C as taught by Iakobashvili et al. for the purpose of developing an improved sensitive and rapid method for primer extension and amplification of the target. One skilled in the art would be motivated to combine the method as disclosed by Hong et al. with the inclusion temperature conditions as taught Iakobashvili et al. because Iakobashvili et al. explicitly taught thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said temperature conditions would result in a rapid PCR and sequencing analysis at low amount of target DNA and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

B. Claims 1-3, 6-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 of U.S. Patent No. 5,747,298 ('298) in view of Iakobashvili et al. (Nucleic Acids Research, Vol. 27, No.6, page 1566-1568, 1999, the reference taken from the IDS submitted on April 4, 2005, by Applicants).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-3, 6-7 are drawn to a method fro extending an oligonucleotide primer or a primer pair using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C, comprising (i) mixing a template DNA with a primer or a pair of primers, and a natural or modified form of a moderately thermostable DNA polymerase selected from the group consisting of Bacillus stearothermophilus, Bacillus caldotenax and Bacillus caldolyticus, wherein the DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminus of the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template, in a solution containing between 10% and about 20% (v/v) glycerol, ethylene glycol, or a mixture of glycerol and ethylene glycol, under conditions that the cycle reaction temperature fluctuates between a melting temperature of about 70^0 C, and an annealing temperature of about 37^0 C, and repeating the cycle primer extension at least two times and until the DNA polymerase repeatedly extends the primer or primer pair of primers to produce a sequence-specific amplification product of a desired length and use of forward and reverse primers.

Claims 1-3, 6-7 of the instant invention fall with in the scope of the claims 6 of the patent ('298), because the claim 6 of the patent disclose said method for extending a primer or primers using a DNA polymerase having 3'-5' exonuclease activity and said DNA polymerase has 3'-5' proof reading activity as recited in the instant application. The method of the patented claim differ from the instant claims in that, it fails to disclose primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C, under conditions that the cycle reaction temperature fluctuates between a melting temperature of about 70^0 C, and an annealing temperature of about 37^0 C, and repeating the cycle primer extension at least two times and until the DNA polymerase repeatedly extends the primer or primer pair of primers to produce a sequence-specific amplification product of a desired length.

Iakobashvili et al. teach a method for extending an oligonucleotide primer or primers using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C (see page 1567, col. 1, Fig. 3, line 1-23 of the legend, indicates melting temperature as 70^0 C and annealing at 37^0 C), comprising the step of mixing a template DNA with primers and a DNA polymerase having proofreading 3'-5' exonuclease activity (which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand) (see page 1567, col. Fig. 3 legend) in a solution containing glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig. 3 legend, which meets the limitations between about 10% and about 20% v/v), under conditions that cycle reaction temperature fluctuates between a melting temperature of about 70^0 C and an annealing temperature about 37^0 C (see page 1567, col. 1, line 21-22 of Fig. 3 legend) and repeating the cycle primer extension reaction at least two times (repeated 35 cycles) and until the DNA polymerase repeatedly extends the

primers to produce a sequence-specific amplification product of a desired length (see page 1567, col. 1, line 21-23 of Fig. 3 legend and also see the Fig .3 for the desired length of sequence-specific product). Iakobashvili et al. teach that the method comprises about 15 % glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig.3, legend, which meets the limitation of about 15%); With regard to claim 6-7, Iakobashvili et al teach use of a forward and a reverse primer to amplify a selected segment of the template by repeated heating and cooling cycles (see page 1567, col. 1, Fig. 3, line 1-9 of the legend); that primers may be of varying length (see page 1566, col. 1, paragraph 3, col. 2, line 1- 14, page 1567, Fig. 4 legend).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for extending an oligonucleotide primer as disclosed by Hong et al. with the temperature conditions ranging between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C as taught by Iakobashvili et al. for the purpose of developing an improved sensitive and rapid method for primer extension and amplification of the target. One skilled in the art would be motivated to combine the method as disclosed by Hong et al. with the inclusion temperature conditions as taught Iakobashvili et al. because Iakobashvili et al. explicitly taught thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said temperature conditions would result in a rapid PCR and sequencing analysis at low amount of target DNA and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

C. Claims 1-4, 6-11, 22-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 of U.S. Patent No. 6,485,909 ('909) in view of Iakobashvili et al. (Nucleic Acids Research, Vol. 27, No.6, page 1566-1568, 1999, the reference taken from the IDS submitted on April 4, 2005, by Applicants).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-4, 6-8, 28-29 are drawn to a method fro extending an oligonucleotide primer or a primer pair using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C, comprising (i) mixing a template DNA with a primer or a pair of primers, and a natural or modified form of a moderately thermostable DNA polymerase selected from the group consisting of Bacillus stearothermophilus, Bacillus caldotenax and Bacillus caldolyticus, wherein the DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminus of the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template, in a solution containing between 10% and about 20% (v/v) glycerol, ethylene glycol, or a mixture of glycerol and ethylene glycol, under conditions that the cycle reaction temperature fluctuates between a melting temperature of about 70^0 C, and an annealing temperature of about 37^0 C, and repeating the cycle primer extension at least two times and until the DNA polymerase repeatedly extends the primer or primer pair of primers to produce a sequence-specific amplification product of a desired length and use of forward and reverse primers. Claims 9-11, 22-23, 30-31 are drawn to a method for extending a primer or

primers using ddNTPs, their analogs and dye-labeled terminators. Claims 24-27, 32-35 are drawn to a DNA polymerase comprising SEQ ID Nos. 3 and 4.

Claims 1-4, 6-11, 22-23, 28-31 of the instant invention fall with in the scope of the claims 1-2, 6-8, 11-13, 16-20, 24-26 of the patent ('909), because the claims of the patent disclose said method for extending a primer or primers using a DNA polymerase having 3'-5' exonuclease activity and said DNA polymerase has 3'-5' proof reading activity, sequencing using ddNTPs, their analogs and dye-labeled terminators as recited in the instant application. Further the instant claims 24-27, 32-35 fall within the scope of claims 3-5, 9-10, 13-15, 21-23 of the patent. The patented claims differ from the instant claims in that the patented claims fail to disclose primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C, under conditions that the cycle reaction temperature fluctuates between a melting temperature of about 70^0 C, and an annealing temperature of about 37^0 C, and repeating the cycle primer extension at least two times and until the DNA polymerase repeatedly extends the primer or primer pair of primers to produce a sequence-specific amplification product of a desired length.

Iakobashvili et al. teach a method for extending an oligonucleotide primer or primers using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C (see page 1567, col. 1, Fig. 3, line 1-23 of the legend, indicates melting temperature as 70^0 C and annealing at 37^0 C), comprising the step of mixing a template DNA with primers and a DNA polymerase having proofreading 3'-5' exonuclease activity (which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand) (see page 1567, col. Fig. 3 legend) in a solution containing glycerol (12.5% to

17% w/v) (see page 1567, col. 1, line 9-18 of Fig. 3 legend, which meets the limitations between about 10% and about 20% v/v), under conditions that cycle reaction temperature fluctuates between a melting temperature of about 70^0 C and an annealing temperature about 37^0 C (see page 1567, col. 1, line 21-22 of Fig. 3 legend) and repeating the cycle primer extension reaction at least two times (repeated 35 cycles) and until the DNA polymerase repeatedly extends the primers to produce a sequence-specific amplification product of a desired length (see page 1567, col. 1, line 21-23 of Fig. 3 legend and also see the Fig .3 for the desired length of sequence-specific product). Iakobashvili et al. teach that the method comprises about 15 % glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig.3, legend, which meets the limitation of about 15%); With regard to claim 6, Iakobashvili et al teach use of a forward and a reverse primer to amplify a selected segment of the template by repeated heating and cooling cycles (see page 1567, col. 1, Fig. 3, line 1-9 of the legend); that primers may be of varying length (see page 1566, col. 1, paragraph 3, col. 2, line 1- 14, page 1567, Fig. 4 legend).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for extending an oligonucleotide primer as disclosed by Hong et al. with the temperature conditions ranging between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C as taught by Iakobashvili et al. for the purpose of developing an improved sensitive and rapid method for primer extension and amplification of the target. One skilled in the art would be motivated to combine the method as disclosed by Hong et al. with the inclusion temperature conditions as taught Iakobashvili et al. because Iakobashvili et al. explicitly taught thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR

and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said temperature conditions would result in a rapid PCR and sequencing analysis at low amount of target DNA and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim interpretation: in the following rejections the term "about" is broader in scope and can include any number around the given range of temperature or concentration of glycerol. Further the instant claims recite annealing temperature of about 37^0 C, which supports the range recited in the preamble is broader by +/- 10^0 C.

A. Claims 1-4, 6-11, 18-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong et al. (USPN. 5,834,253) in view of Iakobashvili et al. (Nucleic Acids Research, Vol.

27, No.6, page 1566-1568, 1999, the reference taken from the IDS submitted on April 4, 2005, by Applicants).

With reference to the instant claims 1-4, 6-10, 22-23, 28-31, Hong et al. teach a method for extending an oligonucleotide primer annealed to a DNA template (double-stranded or single-stranded DNA) for direct cycle sequencing (classic Sanger one-step reaction) at temperatures between 45 C and 65 C and a melting temperature below about 80 C (see column 5, lines 1-17, column 12, lines 1-67, column 13, lines 1-7, column 18, lines 60-67, column 19, lines 1-49, column 20, lines 1-21) comprising (i) mixing a template with a primer (sequencing primer), four standard dNTP , ddNTP terminators or their analogs, a DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminusof the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template in a solution containing between about 10% and about 20% (see col.19, line 7-12, indicates 1.0 ul of solution containing 50% glycerol is used in a reaction volume of 2.5 ul in the primer extension step (final concentration in 2.5ul reaction mix will be about 18%, which indicates the final concentration of glycerol in the reaction meets the range limits as recited in the instant claims), under conditions that DNA polymerase extends the primer (see column 5, lines 2-12); (ii) effecting cycle primer extension reaction at temperature below 80^0 C and more active at 65^0 C (column 12, lines 46-55).

With regard to claims 11, 18-21, 24-27, 32-35, Hong et al. also teach that the DNA polymerase comprises DNA polymerase having homology (99-100%) to the instant claimed SEQ ID Nos. 1-4 (see sequence listing of patent '253 and attached sequence alignment);

With regard to claims 22-23, 30-31, Hong et al. also teach use of fluorescent dye labeled nucleotides (see column 13, lines 1-7);

With regard to claims 22-23, 30-31, Hong et al. also teach that said DNA polymerase reduces the innate selective discrimination against the incorporation of nucleotide analogs such as ddNTPs, dITP and 7-deaza-dGTP (see column 12, lines 56-64).

However, Hong et al. did not teach melting temperature about 70^0 and annealing temperature about 37^0 C.

Iakobashvili et al. teach a method of claim 1, 3, 9-10, 22-23, 30-31, a method for extending an oligonucleotide primer or primers using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C (see page 1567, col. 1, Fig. 3, line 1-23 of the legend, indicates melting temperature as 70^0 C and annealing at 37^0 C), comprising the step of mixing a template DNA with primers and a DNA polymerase having proofreading 3'-5' exonuclease activity (which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand) (see page 1567, col. Fig.3 legend) in a solution containing glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig. 3 legend, which meets the limitations between about 10% and about 20% v/v), under conditions that cycle reaction temperature fluctuates between a melting temperature of about 70^0 C and an annealing temperature about 37^0 C (see page 1567, col. 1, line 21-22 of Fig. 3 legend) and repeating the cycle primer extension reaction at least two times (repeated 35 cycles) and until the DNA polymerase repeatedly extends the primers to produce a sequence-specific amplification product of a desired length (see page 1567, col. 1, line 21-23 of Fig. 3 legend and also see the Fig .3 for the desired length of sequence-specific product).

With regard to claim 2, Iakobashvili et al. teach that the method comprises about 15 % glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig.3, legend, which meets the limitation of about 15%);

With regard to claim 6, Iakobashvili et al teach use of a forward and a reverse primer to amplify a selected segment of the template by repeated heating and cooling cycles (see page 1567, col. 1, Fig. 3, line 1-9 of the legend);

With regard to claim 7-8, Iakobashvili et al. teach primers may be of varying length (see page 1566, col. 1, paragraph 3, col. 2, line 1- 14, page 1567, Fig. 4 legend).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for extending an oligonucleotide primer as disclosed by Hong et al. with the temperature conditions ranging between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C as taught by Iakobashvili et al. for the purpose of developing an improved sensitive and rapid method for primer extension and amplification of the target. One skilled in the art would be motivated to combine the method as disclosed by Hong et al. with the inclusion temperature conditions as taught Iakobashvili et al. because Iakobashvili et al. explicitly taught thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said temperature conditions would result in a rapid accurate PCR and sequencing analysis at low amount of target DNA and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

B. Claims 1-3, 6-10, 22-23, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong et al. (USPN. 5,747,298) ('298) in view of Iakobashvili et al. (Nucleic Acids Research, Vol. 27, No.6, page 1566-1568, 1999, the reference taken from the IDS submitted on April 4, 2005, by Applicants).

With reference to the instant claims 1-3, 6-10, 22-23, 28-31, Hong et al. teach a method for extending an oligonucleotide primer annealed to a DNA template (double-stranded or single-stranded DNA) for direct cycle sequencing at temperatures between 45 C and 65 C and a melting temperature below about 80 C (see col. 5, line 10-37, col. 8, line 1-67, col. 9, line 1-15) comprising (i) mixing a template with a primer (sequencing primer), four standard dNTPs, ddNTP terminators or their analogs, a DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminusof the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template (col. 5, line 27-37) in a solution containing between about 10% and about 20% glycerol, ethylene glycol, or a mixture of glycerol and ethylene glycol (see col. 8, line 17-22, indicates 1.0 ul of solution containing 50% glycerol is used in a reaction volume of 2.5 ul in the primer extension step (final concentration in 2.5ul reaction mix will be about 18%, which indicates the final concentration of glycerol in the reaction meets the range limits as recited in the instant claims) under conditions that DNA polymerase extends the primer (see col. 8, line 1-64); (ii) effecting cycle primer extension reaction at temperature below 80^0 C and more active at 65^0 C (column 8, line 14-67, col. 9, line 1-6, lines 46-55).

With regard to claims 22-23, 30-31, Hong et al. also teach use of fluorescent dye labeled nucleotides (see column 5, lines 55-65);

With regard to claims 22-23, 30-31, Hong et al. also teach that said DNA polymerase reduces the innate selective discrimination against the incorporation of nucleotide analogs such as ddNTPs, dITP and 7-deaza-dGTP (see column 5, lines 47-55, col. 9, line 1-6).

However, Hong et al. did not teach melting temperature about 70^0 and annealing temperature about 37^0 C.

Iakobashvili et al. teach a method of claim 1, 3, 9-10, 22-23, 30-31, a method for extending an oligonucleotide primer or primers using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C (see page 1567, col. 1, Fig. 3, line 1-23 of the legend, indicates melting temperature as 70^0 C and annealing at 37^0 C), comprising the step of mixing a template DNA with primers and a DNA polymerase having proofreading 3'-5' exonuclease activity (which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand) (see page 1567, col. Fig.3 legend) in a solution containing glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig. 3 legend, which meets the limitations between about 10% and about 20% v/v), under conditions that cycle reaction temperature fluctuates between a melting temperature of about 70^0 C and an annealing temperature about 37^0 C (see page 1567, col. 1, line 21-22 of Fig. 3 legend) and repeating the cycle primer extension reaction at least two times (repeated 35 cycles) and until the DNA polymerase repeatedly extends the primers to produce a sequence-specific amplification product of a desired length (see page 1567, col. 1, line 21-23 of Fig. 3 legend and also see the Fig .3 for the desired length of sequence-specific product).

With regard to claim 2, Iakobashvili et al. teach that the method comprises about 15 % glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig.3, legend, which meets the limitation of about 15%);

With regard to claim 6, Iakobashvili et al teach use of a forward and a reverse primer to amplify a selected segment of the template by repeated heating and cooling cycles (see page 1567, col. 1, Fig. 3, line 1-9 of the legend);

With regard to claim 7-8, Iakobashvili et al. teach primers may be of varying length (see page 1566, col. 1, paragraph 3, col. 2, line 1- 14, page 1567, Fig. 4 legend).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for extending an oligonucleotide primer as disclosed by Hong et al. with the temperature conditions ranging between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C as taught by Iakobashvili et al. for the purpose of developing an improved sensitive and rapid method for primer extension and amplification of the target. One skilled in the art would be motivated to combine the method as disclosed by Hong et al. with the inclusion temperature conditions as taught Iakobashvili et al. because Iakobashvili et al. explicitly taught thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said temperature conditions would result in a rapid accurate PCR and sequencing analysis at low amount of target DNA and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

C. Claims 1-4, 6-11, 18-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong et al. (USPN. 6,485,909) ('909) in view of Iakobashvili et al. (Nucleic Acids Research, Vol. 27, No.6, page 1566-1568, 1999, the reference taken from the IDS submitted on April 4, 2005, by Applicants).

With reference to the instant claims 1-3, 6-10, 22-23, 28-31, Hong et al. teach a method for extending an oligonucleotide primer annealed to a DNA template (double-stranded or single-stranded DNA) for direct cycle sequencing at temperatures between 45^0 C and 65^0 C (see col. 10, line 49-64, col. 15, line 60-67, col. 16, line 1-30) comprising (i) mixing a template with a primer (sequencing primer), four standard dNTPs, ddNTP terminators or their analogs, a DNA polymerase which has proof-reading 3'-5' exonuclease activity, such that the DNA polymerase functions to excise mismatched nucleotides from 3'-terminusof the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template (col. 10, line 66-67, col. 11, line 1-11) in a solution containing between about 10% and about 20% glycerol, ethylene glycol, or a mixture of glycerol and ethylene glycol (see col. 23, line 9-36, col. 28, line 9-37, indicates 4.0 ul of solution containing 50% glycerol is used in a reaction volume of 20 ul in the primer extension step (final concentration in 20 ul reaction mix will be about 10 %, which indicates the final concentration of glycerol in the reaction meets the range limits as recited in the instant claims) under conditions that DNA polymerase extends the primer (see col. 28, line 14-36); (ii) effecting cycle primer extension reaction at temperature below 80^0 C and more active at 65^0 C (column 28, line 14-67).

With regard to claims 4, 11, 18-21, 24-27, 32-35, Hong et al. also teach that the DNA polymerase comprises DNA polymerase having homology (99-100%) to the instant claimed SEQ ID Nos. 1-4 (see sequence listing of patent '909 and attached sequence alignment);

With regard to claims 22-23, 30-31, Hong et al. also teach use of fluorescent dye labeled nucleotides (see column 18, line 40-67);

With regard to claims 22-23, 30-31, Hong et al. also teach that said DNA polymerase reduces the innate selective discrimination against the incorporation of nucleotide analogs such as ddNTPs, dITP and 7-deaza-dGTP (see column 8, lines 25-38).

However, Hong et al. did not teach melting temperature about 70^0 and annealing temperature about 37^0 C.

Iakobashvili et al. teach a method of claim 1, 3, 9-10, 22-23, 30-31, a method for extending an oligonucleotide primer or primers using an enzymatic cycle primer extension reaction at temperatures between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C (see page 1567, col. 1, Fig. 3, line 1-23 of the legend, indicates melting temperature as 70^0 C and annealing at 37^0 C), comprising the step of mixing a template DNA with primers and a DNA polymerase having proofreading 3'-5' exonuclease activity (which functions to excise mismatched nucleotides from the 3' terminus of the DNA strand) (see page 1567, col. Fig.3 legend) in a solution containing glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig. 3 legend, which meets the limitations between about 10% and about 20% v/v), under conditions that cycle reaction temperature fluctuates between a melting temperature of about 70^0 C and an annealing temperature about 37^0 C (see page 1567, col. 1, line 21-22 of Fig. 3 legend) and repeating the cycle primer extension reaction at least two times (repeated 35 cycles) and

until the DNA polymerase repeatedly extends the primers to produce a sequence-specific amplification product of a desired length (see page 1567, col. 1, line 21-23 of Fig. 3 legend and also see the Fig .3 for the desired length of sequence-specific product).

With regard to claim 2, Iakobashvili et al. teach that the method comprises about 15 % glycerol (12.5% to 17% w/v) (see page 1567, col. 1, line 9-18 of Fig.3, legend, which meets the limitation of about 15%);

With regard to claim 6, Iakobashvili et al teach use of a forward and a reverse primer to amplify a selected segment of the template by repeated heating and cooling cycles (see page 1567, col. 1, Fig. 3, line 1-9 of the legend);

With regard to claim 7-8, Iakobashvili et al. teach primers may be of varying length (see page 1566, col. 1, paragraph 3, col. 2, line 1- 14, page 1567, Fig. 4 legend).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method for extending an oligonucleotide primer as disclosed by Hong et al. with the temperature conditions ranging between about 45^0 C and about 65^0 C and a melting temperature of about 70^0 C as taught by Iakobashvili et al. for the purpose of developing an improved sensitive and rapid method for primer extension and amplification of the target. One skilled in the art would be motivated to combine the method as disclosed by Hong et al. with the inclusion temperature conditions as taught Iakobashvili et al. because Iakobashvili et al. explicitly taught thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said temperature conditions would result in a

a rapid accurate PCR and sequencing analysis at low amount of target DNA and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

Response to arguments:

7. With regard to the rejection under 35 USC 112, first paragraph (written description), Applicants' arguments are fully considered and found unpersuasive. Applicants agrue that the instant specification describes in some detail the use DNA polymerases from all the three strains of Bacillus and their proofreading exonuclease activity at optimum temperatures and also argue that with these specific information it is not overreaching to cover DNA polymerases having amino acid sequences that shares not less than 95% homology. Applicants' arguments are fully considered and found unpersuasive. Examiner notes that the specification on page 15-16 and 19 describe one species of the genus of DNA polymerases (Bst 320) having homology with naturally occurring DNA polymerases and indicates that other DNA polymerases derived from other strains of Bacillus stearothermophilus, Bacillus caldotenax and Bacillus caldolyticus may be easily modified using conventional DNA modification techniques. Thus the specification describes one species of the genus, that is Bst320 and does not describe any structural limitations of DNA polymerases derived from other strins of Bacillus. Page 19 of the specification describes that the DNA sequences and amino acid sequences include allelic variations and mutations, encompassing non-critical substitutions of nucleotides or amino acids that would not change functionality. Thus the specification does not describe the genus of such fragments or variants (derived by substitution, deletion, or insertion) containing the DNA polymerase activity,

which encompass different structural limitations, for which, no support is provided in the specification.

In this application at the time of filing, there is no record or description, which would demonstrate conception or written description of any structural information of DNA polymerase from any other strain as recited in the instant claims, except for the DNA polymerase from Bst strain 320, with retaining correlative function in the claimed product. Further with regard to DNA polymerases having not less that 95% homology, the specification does not support the large number fragments having no less than 95% homology derived from the three Bacillus strains.

Applicants also argue that the patents issued by USPTO to inventor Dr. Hong include claims to the three mesophilic stains and to DNA polymerases having 95% homology and therefore the instant application has similar breadth to that of the two issued patents. Applicants' arguments are fully considered and found unpersuasive because the instant application do not claim any priority benefit to the issued patents and the instant application is treated on its own merits. Accordingly the scope of the instant claims are different from that of the claims in the issued patents. Therefore the rejection is maintained herein.

8. With regard to the rejections under obviousness double-patenting and 35 USC 103(a) Applicants' arguments and amendment are fully considered and found unpersuasive because the amendment reciting primers less than 30 bases in length and the motivation to combine the Iakobashvilli and Lapidot is different from the Applicants' arguments directed towards the length of the primers. The primary references used in all the rejections above teach a primer less than 30 bases in length and as discussed in the above rejections, Iakobashvili et al. explicitly taught

thermolabile DNA polymerases effectively extends a primer or primers at low temperature conditions utilizing a rather low amount of a source DNA and their use in PCR and sequencing reactions (see page 1568, col. 1, paragraph 1). The ordinary artisan would have a reasonable expectation of success that inclusion of said inherent property of the thermolabile DNA polymerases, that is, temperature conditions at which said DNA polymerases are most effective in extending a primer would result in a rapid accurate PCR and sequencing analysis at low amount of target DNA since Iakobashvilli et al. taught that the thermolabile DNA polymerases would effectively work at low temperatures and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations. Therefore the rejections are maintained herein.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
10/4/05